

Review

Optimizing antibiotic therapy in the intensive care unit setting

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Published online: 28 June 2001

Critical Care 2001, **5**:189–195

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Abstract

Antibiotics are one of the most common therapies administered in the intensive care unit setting. In addition to treating infections, antibiotic use contributes to the emergence of resistance among pathogenic microorganisms. Therefore, avoiding unnecessary antibiotic use and optimizing the administration of antimicrobial agents will help to improve patient outcomes while minimizing further pressures for resistance. This review will present several strategies aimed at achieving optimal use of antimicrobial agents. It is important to note that each intensive care unit should have a program in place which monitors antibiotic utilization and its effectiveness. Only in this way can the impact of interventions aimed at improving antibiotic use (e.g. antibiotic rotation, de-escalation therapy) be evaluated at the local level.

Keywords antibiotics, infections, intensive care, treatment

There is general consensus that in-hospital antimicrobial resistance influences patient outcome and the allocation of resources [1]. Antibiotic resistance is occurring more rapidly and more frequently all over the world, with Gram-negative bacilli and Gram-positive bacteria being important causes of hospital-acquired infections [2,3]. In many cases, there are few effective antimicrobial agents, particularly with methicillin-resistant and vancomycin-resistant *Staphylococcus aureus* and Gram-negative bacteria [4,5].

This review will focus on strategies aimed at optimizing antibiotic use within intensive care units. This is an important issue for intensivists because of the acute nature of critically ill patients and the increased likelihood of antimicrobial resistance within intensive care units [6,7]. There are numerous pressures within intensive care units that potentiate the emergence of antibiotic-resistant infections: the frequent use of broad spectrum antibiotics, the crowding of patients with complex medical problems into small areas of the hospital, and the presence of more chronically and acutely ill patients who require prolonged hospitaliza-

tions and often harbour antibiotic-resistant bacteria [8,9]. Furthermore, reductions in nursing and other staff through economic pressures increase the likelihood of person-to-person transmission.

Preventing nosocomial infections is important to reduce the use of antibiotics [1]. Many hospitals have reduced the number of nosocomial infections through infection control programmes and novel interventions [10,11]. By optimizing the use of antibiotics within intensive care units, patient outcomes are improved, better initial antibiotic administration is provided, and the chances of further antibiotic resistance are minimized [12–14]. In addition to the strategies described in this review (Table 1), clinicians must insure that antibiotic administration satisfies minimal requirements, such as proper dosing, drug interval administration, monitoring drug levels, and avoiding harmful drug interactions. Not satisfying these minimal requirements will lead to patients receiving suboptimal antibiotic concentrations, which increases the likelihood of treatment failures, antibiotic resistance, and patient toxicity [15,16].

Table 1

Practices promoting the optimization of antimicrobial use in the intensive care unit setting

- Provide adequate initial treatment of serious infections (e.g. pneumonia, bloodstream)
- Awareness of predominant causative pathogens
- Up to date unit-specific pathogen antibiograms
- Drainage of abscesses, empyema cavities, other infected fluid collections
- Removal of infected foreign bodies (e.g. central venous catheters)
- Monitor serum drug concentrations when appropriate to achieve therapeutic levels
- Minimize antibiotic pressures promoting resistance
- Avoid prolonged courses of empiric antibiotic therapy
- Consider de-escalation of antibiotics based on available microbiologic data and clinical course
- Use narrow spectrum antibiotics when supported by clinical situation and culture data
- Establish appropriate thresholds for prescribing antibiotics
- Develop predetermined criteria for the discontinuation of antimicrobial therapy

Antimicrobial optimization strategies

Guidelines/protocols

Antibiotic administration guidelines/protocols developed locally or by national societies potentially avoid unnecessary antibiotic administration and increase therapeutic effectiveness. Unfortunately, even well-developed guidelines/protocols may not translate into widely accepted treatment algorithms. Some deviation from guidelines/protocols is expected because medical decision-making should be guided by an individual patient's characteristics and the judgement and experience of the caregivers. Locally developed guidelines therefore often have the best chance of being accepted by local health care providers and hence of being implemented [17].

The potential benefits of guidelines/protocols have been well demonstrated by the Latter Day Saints Hospital in Salt Lake City, Utah, where a computerized system guides antibiotic administration. The system automatically identifies and minimizes adverse drug effects due to antibiotics [18,19] and has reduced inadequate administration compared with physician prescribing patterns [20]. The system has also been associated with stable antibiotic susceptibility patterns over time, both for Gram-positive and Gram-negative bacteria [21]. It has most recently been shown to significantly reduce orders for drugs to which patients were allergic, the number of adverse events caused by antibiotics, and the total number of antibiotic doses prescribed, as well as the medical costs associated with antimicrobial agents [22].

Non-automated or partially automated systems, usually driven by hospital-based quality improvement teams, have demonstrated similar results [23]. Bailey *et al* randomized patients so that pharmacists contacted some of their

physicians with recommendations for discontinuing intravenous antibiotics [24]. The pharmacists' intervention significantly reduced antibiotic doses and mean antibiotic costs, but was associated with increased labour costs. Similarly, Leibovici *et al* developed a problem-oriented decision support system that significantly reduced the injudicious or inadequate administration of antibiotics, particularly in patients infected with multiresistant Gram-negative isolates, enterococci, and *S. aureus* [25]. As technology, such as handheld computers and portable communication devices, becomes widely available there is more opportunity to influence treatment protocols.

Two groups of investigators recently demonstrated the use of protocols/guidelines for the management of ventilator-associated pneumonia (VAP). Singh *et al* used a scoring system to identify patients with suspected VAP who could be treated with 3 days of antibiotics as opposed to the conventional practice of 10–21 days [26]. Patients receiving the shorter course had similar clinical outcomes to the patients receiving the longer course but with fewer subsequent superinfections attributed to antibiotic-resistant pathogens. Ibrahim *et al* employed a pharmacist-directed protocol in intensive care units to reduce the administration of antibiotics for suspected VAP to 8.1 ± 5.1 days from 14.8 ± 8.1 days ($P < 0.001$) [27].

Restricting the hospital formulary

Restricting the use of certain antibiotics or classes of antibiotics has been shown to reduce pharmacy expenses and adverse drug reactions from the restricted drug or drugs [28]. This approach is generally applied to drugs with broad spectrums of action (such as imipenem), where antibiotic resistance emerges rapidly (as with third-generation cephalosporins) and where toxicity is readily identified

(such as with aminoglycosides). However, not all experiences have been uniformly successful. One survey of 88 hospitals found that the average total expenditure on antimicrobial agents between 1993 and 1994 increased by \$300 per occupied bed, despite over 60% of the hospitals restricting the use of antibiotics [29]. Of the 88 hospitals, only 7% decreased costs by \$500 or more per occupied bed. The most common reasons for these decreases were restructuring of pricing contracts and education programmes aimed at reducing the use of antibiotics. Replacing one antimicrobial with another only lead to increased use of other antimicrobials, rather than the replacement, and did not produce any savings. Furthermore, restricting the use of certain antimicrobials can promote antibiotic resistance to other antimicrobials [30].

To date, mainly due to methodological problems, it has been difficult to demonstrate that restricting hospital formularies is effective in curbing the emergence of resistance or improving antimicrobial efficacy. However, the restrictions have been successful in outbreaks of infection with antibiotic-resistant bacteria, particularly in conjunction with infection control practices and antibiotic educational activities.

Hospitals in Greece during the late 1980s had high levels of antimicrobial resistance among Gram-negative bacteria, particularly in *Enterobacter*, *Klebsiella*, and *Acinetobacter* species, and *Pseudomonas aeruginosa* [31]. To combat this, one hospital introduced a structured programme involving: specific rules for hospital hygiene; educational programmes for small groups of healthcare providers; and an antibiotic policy aimed at restricting their overall use, especially those with broad spectra. Imipenem, the newer fluoroquinolones, vancomycin, aztreonam, and the third-generation cephalosporins could only be ordered with a specific antibiotic request form that, from 1991 onwards, had to be approved by an infectious diseases specialist. A 3-year audit between 1992 and 1995 demonstrated decreased use of the restricted antibiotics compared with that before 1991, without there being an increase in the use of non-restricted antibiotics. There was also an associated reduction in antimicrobial resistance, except resistance to fluoroquinolones, which were subsequently removed from the hospital's formulary. All this was achieved despite increasing levels of antimicrobial resistance across Europe during the same time [2,3].

Outbreaks of diarrhoea associated with *Clostridium difficile* are often linked to antibiotic use and misuse. In one experience, an outbreak that was caused by a clonal isolate of clindamycin-resistant *C. difficile* was associated with increased use of clindamycin despite the presence of infection control practices [32]. To restrict the use of clindamycin, all requests for its use had to be approved by a consultant in infectious diseases. This resulted in an overall reduction in its use, a sustained reduction in the

mean number of cases of diarrhoea associated with *C. difficile*, and an increase in clindamycin susceptibility among *C. difficile* strains. Although this led to increased use of antibiotics with anti-anaerobic activity, including cefotetan, ticarcillin-clavulonate, and imipenem, the hospital saved money as a result of the decreased incidence of diarrhoea associated with *C. difficile*.

Restricting hospital formularies may be useful in the control of outbreaks due to specific bacterial pathogens or when other infection control practices have been unsuccessful. They cannot, however, be viewed as an alternative to judicious use of antibiotics, since resistance is likely to develop in the antibiotics that are not restricted [30,33].

Scheduled changes in antibiotic

To combat an outbreak of infection from extended spectrum B-lactamase-producing *Klebsiella*, Rahal *et al* introduced an antibiotic guideline into their hospital that significantly restricted the use of cephalosporins [30]. The use of cephalosporins was reduced by 80.1%, which was accompanied by a 44.0% reduction in infection and colonization with extended spectrum B-lactamase-producing *Klebsiella*. At the same time, however, the use of imipenem increased by 140.6% and was associated with a 68.7% increase in the incidence of imipenem-resistant *P. aeruginosa*.

Kollef *et al* examined the influence of a scheduled change in antibiotic on the incidence of nosocomial infections among patients undergoing cardiac surgery [34]. In the 6 months preceding the surgery, a third-generation cephalosporin (ceftazidime) was used for the treatment of Gram-negative bacterial infections. In the 6 months after the surgery, a fluoroquinolone (ciprofloxacin) was used. Unexpectedly, the overall incidence of VAP was significantly reduced in the 6 months after the surgery compared with the 6 months before, primarily because of a significant reduction in the incidence of VAP attributed to antibiotic-resistant Gram-negative bacteria. A lower incidence of antibiotic-resistant Gram-negative bacteraemia was similarly observed in the 6 months after the surgery. This experience was followed by a series of scheduled antibiotic changes for the treatment of suspected Gram-negative bacterial infections among patients admitted to the medical and surgical intensive care units [35]. Overall, the prescription of adequate antimicrobial therapy was statistically increased for Gram-negative bacterial infections. However, the long-term effectiveness of a limited number of scheduled antibiotic changes is unknown owing to the potential for increased emergence of resistance to the newly selected antibiotic classes [30].

Combining antibiotic therapy

The use of combination antimicrobial therapy has been proposed as a strategy to reduce the emergence of bacterial

resistance, as has been employed for *Mycobacterium tuberculosis* [36]. Unfortunately, no convincing data exist to validate this hypothesis for nosocomial pneumonia [37]. Conclusive data that combination antibiotic therapy for nosocomial bloodstream infections prevents the subsequent emergence of antibiotic resistance is similarly lacking [38]. Nevertheless, there is some indirect evidence that the use of combination antimicrobial therapy may be useful.

In the County of Northern Jutland, Denmark, all bacteraemia were analysed with regard to antibiotic resistance over a 14-year period (1981–1995) [39]. A total of 8840 isolates from 7938 episodes of bacteraemia were identified. The level of resistance to third-generation cephalosporins, carbapenems, aminoglycosides, and fluoroquinolones among Enterobacteriaceae was low (<1%). The recommended regimen for empirical antibiotic treatment in this region is a combination of penicillin G or ampicillin and an aminoglycoside, which provided an overall coverage of 94%. This experience suggests that combination therapy with narrow spectrum agents over prolonged time periods may help curb resistance to broad spectrum antibiotics, yet still provide effective treatment of serious infections to include bacteraemia.

In addition to potentially preventing antibiotic resistance, combination antimicrobial therapy may be more effective for providing adequate initial treatment of resistant pathogens and producing beneficial clinical and microbiologic responses. Trouillet *et al* demonstrated that certain antibiotic combinations were more likely to provide higher rates of bacteriologic cure than other combinations for nosocomial pneumonia within a specific hospital setting [6]. Brun-Buisson *et al* similarly showed that, despite the addition of an aminoglycoside, treatment with ceftazidime was associated with a greater number of bacteriologic failures as compared with piperacillin-tazobactam employed in combination with an aminoglycoside [40].

Antibiotic rotation

The concept of antibiotic class cycling has been advocated as a potential strategy for reducing the emergence of antimicrobial resistance [41]. In theory, a class of antibiotics or a specific antibiotic drug is withdrawn from use for a defined time period and reintroduced at a later point in time in an attempt to limit bacterial resistance to the cycled antimicrobial agents [42]. However, limited clinical data is currently available that has examined the issue of antibiotic class changes or cycling [43].

Gerding *et al* evaluated cycling of aminoglycosides during 10 years at the Minneapolis Veterans Affairs Medical Center, cycling amikacin and gentamicin [44]. Resistance to gentamicin had emerged as a clinical problem limiting the use of that specific aminoglycoside at this hospital. Using cycle times of 12–51 months, these investigators

found significantly reduced resistance to gentamicin when amikacin was used, but a return of resistance with the rapid reintroduction of gentamicin. This was followed by more gradual reintroduction of gentamicin a second time, without increased levels of resistance recurring. This experience suggested that the cycling of antibiotics within the same drug class, in some circumstances, could be an effective strategy for curbing antimicrobial resistance.

Gruson *et al* observed a reduction in the incidence of ventilator-associated pneumonia after introducing an antimicrobial programme that consisted of supervised rotation and restricted use of ceftazidime and ciprofloxacin, which were widely prescribed before institution of the antibiotic programme [45]. The antibiotic selection was based on monthly reviews of the pathogens isolated from the intensive care unit and their antibiotic susceptibility patterns. These clinicians were therefore rotating antimicrobial agents based on 'real-time' information that allowed potentially more effective antibiotics to be prescribed to their patients. They observed a decrease in the incidence of ventilator-associated pneumonia that was primarily due to a reduction in the number of episodes attributed to potentially antibiotic-resistant Gram-negative bacteria, including *P. aeruginosa*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *Acinetobacter baumannii*.

Area-specific antimicrobial therapy

Variability in the pathogens associated with nosocomial infections among hospitals, along with their antibiotic susceptibility profiles, has been demonstrated to occur [46]. Additionally, changing temporal patterns of nosocomial pathogens and antimicrobial susceptibility over time have been described [30,47]. This suggests that hospitals may need to develop systems for reporting antimicrobial susceptibility patterns of bacterial pathogens for individual hospital areas or units on a regular basis because of the potential existence of intrahospital variations. Using such data can improve the efficacy of antimicrobial therapy by increasing the likelihood for adequate initial treatment of infections [6].

Antimicrobial de-escalation

There is increasing clinical evidence suggesting that failure to initially treat high-risk microbiologically documented infections (e.g. hospital-acquired pneumonia, bacteraemia) with an adequate initial antibiotic regimen is associated with greater patient morbidity and mortality [12–14]. Inadequate initial antibiotic treatment is usually defined as either the absence of antimicrobial agents directed against a specific class of microorganisms (e.g. absence of therapy for fungaemia due to *Candida albicans*) or the administration of antimicrobial agents to which the microorganism responsible for the infection was resistant (e.g. empiric oxacillin treatment of pneumonia subsequently attributed to methicillin-resistant *S. aureus* based on appropriate culture results).

The most common pathogens associated with the administration of inadequate antimicrobial treatment in patients with hospital-acquired pneumonia include potentially antibiotic-resistant Gram-negative bacteria (*P. aeruginosa*, *Acinetobacter* species, *Klebsiella pneumoniae*, and *Enterobacter* species) and *S. aureus*, especially strains with methicillin resistance [12–14]. For patients with hospital-acquired bloodstream infections, antibiotic-resistant Gram-positive bacteria (methicillin-resistant *S. aureus*, vancomycin-resistant enterococci and coagulase-negative staphylococci), *Candida* species and, less commonly, antibiotic-resistant Gram-negative bacteria account for most cases of inadequate antibiotic treatment [48]. Given the increasing rates of nosocomial infections due to antibiotic-resistant bacteria, clinicians should consider the following recommendations for the initial antibiotic treatment of hospital-acquired infections.

Risk stratification should be employed to identify those patients at high risk for infection with antibiotic-resistant bacteria. These risk factors include prior treatment with antibiotics during the hospitalization, prolonged lengths of stay in the hospital, and the presence of invasive devices (e.g. central venous catheters, endotracheal tubes, urinary catheters) [6,7]. Patients at high risk for infection with antibiotic-resistant bacteria should be treated initially with a combination of antibiotics providing coverage for the most likely pathogens to be encountered in that specific intensive care unit setting. Such an approach to initial antibiotic treatment can be potentially modified if specific microorganisms are excluded based on examination of appropriate clinical specimens (e.g. Gram stain of lower respiratory tract specimens). Such empiric therapy should, however, always be modified once the agent of infection is identified or discontinued altogether if the diagnosis of infection becomes unlikely. De-escalation of antibiotic therapy can be thought of as a strategy to balance the need to provide adequate initial antibiotic treatment of high-risk patients with the avoidance of unnecessary antibiotic utilization, which promotes resistance [27]. Application of this strategy should become more feasible and be accepted as the optimal duration of antibiotic therapy for specific indications and risk-stratified patient groups becomes better identified in the hospital setting [26].

Multiple interventions (infection control and antibiotic restriction)

Several recent experiences suggest that infection control practices aimed at preventing horizontal transmission of antibiotic-resistant nosocomial infections may lack success unless they are also coupled with antimicrobial interventions. Quale *et al* found, despite an intensive programme of barrier precautions for patients with vancomycin-resistant enterococci (VRE) (including having VRE-positive patients in single rooms, performing chlorhexidine perineal washes on VRE-positive patients,

using gloves and chlorhexidine soap for hand washing, and eliminating electronic thermometers), that nearly 50% of the inpatients at their hospital were found to have gastrointestinal colonization with VRE [49,50]. In an attempt to control this outbreak, the hospital formulary was altered by restricting the use of vancomycin and third-generation cephalosporins and adding beta-lactamase inhibitors (ampicillin/sulbactam and piperacillin/tazobactam) because of their enhanced activity against enterococcus. The average monthly use of ceftazidime and vancomycin decreased by 55 and 34%, respectively, after 6 months of implementation. This was associated with a decrease in the point prevalence of faecal colonization with VRE from 47 to 15% ($P < 0.001$) as well as a decrease in the number of patients with clinical isolates positive for VRE.

Montecalvo *et al* described the impact of an enhanced programme for the control of VRE infections in the hospital setting [51]. They developed a multifaceted intervention that included cohorting of staff according to patients' VRE status, early infectious disease consultation, isolating patients with known VRE colonization and those whose VRE colonization status was undetermined, and limiting the use of specific antibiotics (e.g. vancomycin, imipenem) in addition to their standard practices. The incidences of VRE infection and colonization were statistically reduced, as was use of the targeted antimicrobial agents. These studies suggest that strategies aimed at curbing unnecessary antibiotic utilization along with implementation of sound infection control practices are most likely to succeed in terms of reducing antimicrobial resistance and enhancing overall antimicrobial efficacy.

Conclusion

Clinicians practising in intensive care units must develop and promote strategies for more effectively employing antimicrobial therapy. The most successful strategies will be multidisciplinary, involving cooperation from the pharmacy, infection control, nursing staff, treating physicians, and infectious disease consultants. Such programmes should also focus both on promoting infection control practices and employing rational antibiotic utilization aimed at minimizing future emergence of resistance.

Competing interests

None declared.

Acknowledgement

Supported in part by the Barnes Jewish Hospital Foundation.

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